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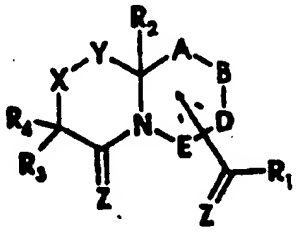
(54) Title: LOW MOLECULAR WEIGHT BICYCLIC THROMBIN INHIBITORS

(57) Abstract

This invention relates to the discovery of heterocyclic competitive inhibitors of the enzyme thrombin having formula (I), their preparation, and pharmaceutical compositions thereof. As well, this invention relates to the use of such compounds and compositions *in vitro* as anticoagulants and *in vivo* as agents for the treatment and prophylaxis of thrombotic disorders such as venous thrombosis, pulmonary embolism and arterial thrombosis resulting in acute ischemic events such as myocardial infarction or cerebral infarction. Moreover, these compounds and compositions have therapeutic utility for the prevention and treatment of coagulopathies associated with coronary bypass operations as well as restenotic events following transluminal angioplasty.



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LOW MOLECULAR WEIGHT BICYCLIC THROMBIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to compounds useful for the treatment of thrombotic disorders, and more particularly to novel heterocyclic inhibitors of the enzyme thrombin.

BACKGROUND

Inordinate thrombus formation on blood vessel walls precipitates acute cardiovascular disease states that are the chief cause of death in economically developed societies. Plasma proteins such as fibrinogen, proteases and cellular receptors participating in hemostasis have emerged as important factors that play a role in acute and chronic coronary disease as well as cerebral artery disease by contributing to the formation of thrombus or blood clots that effectively diminish normal blood flow and supply. Vascular aberrations stemming from primary pathologic states such as hypertension, rupture of atherosclerotic plaques or denuded endothelium, activate biochemical cascades that serve to respond and repair the injury site. Thrombin is a key regulatory enzyme in the coagulation cascade; it serves a pluralistic role as both a positive and negative feedback regulator. However, in pathologic conditions the former is amplified through catalytic activation of cofactors required for thrombin generation as well as activation of factor XIII necessary for fibrin cross-linking and stabilization.

In addition to its direct effect on hemostasis, thrombin exerts direct effects on diverse cell types that support and amplify pathogenesis of arterial thrombus disease. The enzyme is the strongest activator of platelets causing

them to aggregate and release substances (eg. ADP TXA NE) that further propagate the thrombotic cycle. Platelets in a fibrin mesh comprise the principal framework of a white thrombus. Thrombin also exerts direct effects on endothelial cells causing release of vasoconstrictor substances and translocation of adhesion molecules that become sites for attachment of immune cells. In addition, the enzyme causes mitogenesis of smooth muscle cells and proliferation of fibroblasts. From this analysis, it is apparent that inhibition of thrombin activity constitutes a viable therapeutic approach towards the attenuation of proliferative events associated with thrombosis.

The principal endogenous neutralizing factor for thrombin activity in mammals is antithrombin III (ATIII), a circulating plasma macroglobulin having low affinity for the enzyme. Heparin exerts clinical efficacy in venous thrombosis by enhancing ATIII/thrombin binding through catalysis. However, heparin also catalyzes inhibition of other proteases in the coagulation cascade and its efficacy in platelet-dependent thrombosis is largely reduced or abrogated due to inaccessibility of thrombus-bound enzyme. Adverse side effects such as thrombocytopenia, osteoporosis and triglyceridemia have been observed following prolonged treatment with heparin.

Hirudin, derived from the glandular secretions of the leech *hirido medicinalis* is one of the high molecular weight natural anticoagulant protein inhibitors of thrombin activity (Markwardt F. Cardiovascular Drug Reviews, 10, 211, 1992). It is a biopharmaceutical that has demonstrated efficacy in experimental and clinical thrombosis. A potential drawback to the use of Hirudin as a therapeutic agent is likely antigenicity and lack of an effective method of neutralization, especially in view of its extremely tight binding characteristics toward thrombin. The exceedingly high affinity for thrombin is

unique and is attributed to a simultaneous interaction with the catalytic site as well as a distal "anion binding exosite" on the enzyme.

Thrombin activity can also be abrogated by Hirudin-like molecules such as hirulog (Maraganore, J.M. et al., Biochemistry, 29, 7095, 1990) or hirutonin peptides (DiMaio, J. et al., J. Med. Chem., 35, 3331, 1992).

Thrombin activity can also be inhibited by low molecular weight compounds that compete with fibrinogen for thrombin's catalytic site, thereby inhibiting proteolysis of that protein or other protein substrates such as the thrombin receptor. A common strategy for designing enzyme inhibitory compounds relies on mimicking the specificity inherent in the primary and secondary structure of the enzyme's natural substrate. Thus, Blomback et al. first designed a thrombin inhibitor that was modeled upon the partial sequence of the fibrinogen A(B1)α chain comprising its proteolytically susceptible region (Blomback, et al., J. Clin. Lab. Invest., 24, 59, 1969). This region of fibrinogen minimally includes the residues commencing with phenylalanine:

Ala-Asp-Ser-Gly-Glu-Gly-Asp-Phe-Leu-Ala-Glu-Gly
-Gly-Gly-Val-Arg-Gly-Pro-Arg
↑ scissile bond

Systematic replacement of amino acids within this region has led to optimization of the tripeptidyl inhibitory sequence exemplified by the peptide (D)-Phe-Pro-Arg which corresponds to interactions within the P -P -P local binding sites on thrombin (Bajusz S. et al. in Peptides: Chemistry Structure and Biology: Proceedings of the Fourth American

Peptide Symposium, Walter R., Meienhofer J. Eds. Ann Arbor Science Publishers Inc., Ann Arbor MI, 1975, pp 603).

Bajusz et al. have also reported related compounds such as (D)Phe-Pro-Arg-(CO)H (GYKI-14166) and (D)MePhe-Pro-Arg-(CO)H (GYKI-14766) (Peptides-Synthesis, Structure and Function: Proceedings of the Seventh American Peptide Symposium, Rich, D.H. & Gross, E. eds., Pierce Chemical Company , 1981, pp. 417). These tripeptidyl aldehydes are effective thrombin inhibitors both *in vitro* and *in vivo*. In the case of both GYKI-14166 and GYKI-14766, the aldehyde group is presumed to contribute strongly to inhibitory activity in view of its chemical reactivity toward thrombin's catalytic Ser residue, generating a hemiacetal intermediate.

Related work in the area of thrombin inhibitory activity has exploited the basic recognition binding motif engendered by the tripeptide (D)Phe-Pro-Arg while incorporating various functional or reactive groups in the locus corresponding to the putative scissile bond (i.e. P_1-P_1').

In U.S. Patent 4,318,904, Shaw reports chloromethyl-ketones (PPACK) that are reactive towards Ser and His . These two residues comprise part of thrombin's catalytic triad (Bode, W. et al., EMBO Journal 8, 3467, 1989).

Other examples of thrombin inhibitors bearing the (D)Phe-Pro-Arg general motif are those incorporating COOH-terminal boroarginine variants such as boronic acids or boronates (Kettner, C. et al., J. Biol. Chem., 268, 4734, 1993).

Still other congeners of this motif are those bearing phosphonates (Wang, C-L J., Tetrahedron Letters, 33, 7667,

1992) and α-Keto esters (Iwanowicz, E.J. et al.,Bioorganic and Medicinal Chemistry Letters, 12, 1607, 1992).

Neises, B. et al. have described a trichloromethyl ketone thrombin inhibitor (MDL-73756) and Attenburger, J.M. et al. have revealed a related difluoro alkyl amide ketone (Tetrahedron Letters, 32, 7255, 1991).

Maraganore et al. (European 0,333,356; WO 91/02750; U.S. 5,196,404) disclose a series of thrombin inhibitors that incorporate the D-Phe-Pro- moiety and hypothesize that this preferred structure fits well within the groove adjacent to the active site of thrombin. Variations on these inhibitors are essentially linear or cyclic peptides built upon the D-Phe-Pro moiety.

Another series of patents and patent applications have described attempts to develop effective inhibitors against thrombosis by using alpha-ketoamides and peptide aldehyde analogs (EP 0333356;WO 93/15756; WO 93/22344; WO 94/08941; WO 94/17817).

Still others have focused their attention on peptides, peptide derivatives, peptidic alcohols, or cyclic peptides as anti-thrombotic agents (WO 93/22344, EP 0276014; EP 0341607; EP 0291982). Others have examined amidine sulfonic acid moieties to achieve this same end (U.S. 4,781,866), while yet others have examined para or meta substituted phenlyalanine derivatives (WO 92/08709; WO 92/6549).

A series of Mitsubishi patents and patent applications have disclosed apparently effective argininamide compounds for use as antithrombotic agents. The chemical structures described in these documents represent variations of side groups on the argininamide compound (U.S. 4,173,630; U.S.

4,097,591; CA 1,131,621; U.S. 4,096,255; U.S. 4,046,876; U.S. 4,097,472; CA 2,114,153).

Canadian patent applications 2,076,311 and 2,055,850 disclose cyclic imino derivatives that exhibit inhibitory effects on cellular aggregation.

Many of the examples cited above are convergent by maintaining at least a linear acyclic tripeptidyl motif consisting of an arginyl unit whose basic side chain is required for interaction with a carboxylate group located at the base of the P specificity cleft in thrombin. Two adjacent hydrophobic groups provide additional binding through favourable Van der Waals interactions within a contiguous hydrophobic cleft on the enzyme surface designated the P-P site.

One object of the present invention is to provide thrombin inhibitors that display inhibitory activity towards the target enzyme, thrombin.

A further object of the present invention is to provide thrombin inhibitors that display inhibitory activity towards the target enzyme thrombin and are provided for in a pharmacologically acceptable state.

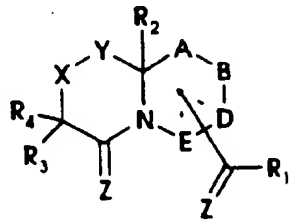
Still a further object of the present invention is to provide for the use of heterocyclic thrombin inhibitors and formulations thereof as anticoagulant and thrombin inhibitory agents.

Yet a further object of the present invention is to provide for the use of heterocyclic thrombin inhibitors and formulations thereof for therapeutic treatment of various thrombotic maladies.

A further object of the present invention is a process for the synthesis of these low molecular weight thrombin inhibitors. The enzyme inhibitors of the present invention are encompassed by the structure of general Formula I.

SUMMARY OF THE INVENTION

The present invention provides for novel compounds that display thrombin inhibitory activity as reflected in formula I:



(I)

wherein:

A is selected from $(CH\text{-}R_6)$, S, SO, SO_2, O and NR wherein R_6 is hydrogen, C_{1-6} alkyl optionally interupted with 1 or 2 heteroatoms; C_{6-10} aryl, C_{3-7} cycloalkyl or heterocyclic ring or a hydrophobic group;

B is selected from S, SO_2, O, -N=, NH, -CH= and CR R wherein R_6 and R_7 are independently selected from hydrogen and C_{1-6} alkyl provided that when A is S, SO, SO_2, O, or NR, then B is CR R;

D is selected from $(CH\text{-}R_5)$ wherein R is hydrogen, C_{1-6} alkyl or $-C(O)R_5$; and CH with a double bond to B when B is -N= or -CH=;

E is selected from CH and CH substituted with the $-C(O)R_5$ provided that only one of D and E is substituted with with $-C(O)R_5$;

X is selected from O, N-R_4, or CH-R_4;

Y is selected from O, S, SO, SO_2, N-R and CH-R provided that when X is N-R_4 then Y is CH-R_4 or O, and when X is O then Y is CH-R_4;

Z is selected from O, S and H;

R_1 is a polar amino acid residuearginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R_2 is selected from H and C alkyl optionally substituted with C aryl, a 6 member heterocycle or a C cycloalkyl ring;

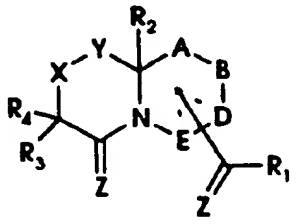
R_3 is selected from H, NR R and C alkyl; and

R_4 and R_5 are independently selected from H; NR R; C aryl or C cycloalkyl optionally substituted with C alkyl; C alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR R or a C aryl, heterocycle or C cycloalkyl group optionally substituted with halogen, hydroxyl, C alkyl; an amino acid side chain; and a hydrophobic group.

As will be appreciated from the disclosure to follow, the molecules, compositions and methods of this invention are useful as anti-coagulants, or in the treatment and prevention of various diseases attributed to the undesirable effects of thrombin, as well as for diagnostic purposes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to molecules which inhibit the enzyme, thrombin. These molecules are characterized by a heterobicyclic moiety as illustrated in Formula I:



(I)

wherein X, Y, Z, A, B, D, E and R to R are as previously defined.

The term "hydrophobic group" (HG) as used hereinafter, refers to any group which lacks affinity for, or displaces water. Hydrophobic groups include but are not limited to C_{1-6} alkyl, C_{2-6} alkenyl (e.g. vinyl, allyl) or C_{2-6} alkynyl (e.g. propargyl) optionally interrupted by a carbonyl group, (e.g. forming an acyl group); C_{6-16} aryl, C_{3-8} cycloalkyl, C_{7-16} aralkyl, C_{4-16} cycloalkyl substituted C_{1-6} alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group (e.g. forming an acyl group) and the ring portion is optionally substituted with C_{1-6} alkyl such as methyl ethyl or t-butyl; or a hydrophobic amino acid side chain. Preferred hydrophobic groups include cyclohexyl, benzyl, benzoyl, phenylmethyl, phenethyl and para-t-butyl-phenylmethyl.

The term "arginyl moiety" represents an arginine amino acid residue or an analogue or derivative thereof. For example, an analogue or derivative of the natural residue may incorporate a longer or shorter methylene chain from the alpha carbon (i.e. ethylene or butylene chain); replacement of the guanidino group with a hydrogen bond donating or accepting group (i.e. amino, amidino or methoxy); replacement of the methylene chain with a constrained group (i.e. an aryl, cycloalkyl or heterocyclic ring); elimination of the terminal carboxyl (i.e. des-carboxy) or hydroxyl (i.e. an aldehyde); or a combination thereof.

The term "alkyl" represents a straight or branched, saturated or unsaturated chain having a specified total number of carbon atoms.

The term "aromatic" or "aryl" represents an unsaturated carbocyclic ring(s) of 6 to 16 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_1R_2) halogen or C_{1-6} alkyl. Aromatic rings include

benzene, napththalene, phenanthrene and anthracene. Preferred aromatic rings are benzene and naphthalene.

The term "cycloalkyl" represents a saturated carbocyclic ring of 3 to 7 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR.R.) halogen or C alkyl. Cycloalkyl groups include cyclo- propyl, butyl, pentyl, hexyl and heptyl. A preferred cycloalkyl group is cyclohexyl.

The term "aralkyl" represents a substituent comprising an aryl moiety attached via an alkyl chain (e.g. benzyl, phenethyl) wherein the sum total of carbon atoms for the aryl moiety and the alkyl chain is as specified. The aryl or chain portion of the group is optionally mono- or di-substituted with OH, SH, amino (i.e. NR R) halogen or C alkyl

The term "heteroatom" as used herein represents oxygen, nitrogen or sulfur (O, N or S) as well as sulfoxyl or sulfonyl (SO or SO) unless otherwise indicated. It is understood that alkyl chains interrupted by one or more heteroatoms means that a carbon atom of the chain is replaced with a heteroatom having the appropriate valency. Preferrably, an alkyl chain is interrupted by 0 to 4 heteroatoms and that two adjacent carbon atoms are not both replaced.

The term "heterocycle" represents a saturated or unsaturated mono- or polycyclic (i.e. bicyclic) ring incorporating 1 or more (i.e. 1-4) heteroatoms selected from N, O and S. It is understood that a heterocycle is optionally mono- or di-substituted with OH, SH, amino (i.e. NR.R.), halogen, CF., oxo or C alkyl. Examples of suitable monocyclic heterocycles include but are not limited to pyridine, piperidine, pyrazine, piperazine, pyrimidine, imidazole, thiazole, oxazole, furan, pyran and

thiophene. Examples of suitable bicyclic heterocycles include but are not limited to indole, quinoline, isoquinoline, purine, and carbazole.

The term "hydrophobic amino acid" represents an amino acid residue that bears an alkyl or aryl group attached to the α-carbon atom. Thus glycine, which has no such group attached to the α-carbon atom is not a hydrophobic amino acid. The alkyl or aryl group can be substituted, provided that the substituent or substituents do not detract from the overall hydrophobic character of the amino acid. Examples of hydrophobic amino acids include natural amino acid residues such as alanine; isoleucine; leucine; phenylalanine; and non-naturally ocurring amino acids such as those described in "The Peptides", vol. 5, 1983, Academic Press, Chapter 6 by D.C. Roberts and F. Vellaccio. Suitable non-naturally ocurring amino acids include cyclohexylalanine and 1-aminocyclohexane-carboxylic.

By "amino acid side chain" is meant the substituent attached to the carbon which is α to the amino group. For example, the side chain of the amino acid alanine is a methyl group and while benzyl is the side chain for phenylalanine.

Preferably R_3 is H or C_{1-4} alkyl. More preferably R_3 is H, methyl or ethyl and most preferably R_3 is H.

Preferably, R_3 is H or C_{1-4} alkyl. More preferably, R_3 is H, methyl or ethyl, and most preferably R_3 is H.

Preferably, one of R_4 or R_5 is a hydrophobic group such as a saturated or unsaturated carbocycle of 5 or 6 members optionally fused to another carbocyclic group while the other is H, C_{1-4} alkyl optionally substituted by NR_2R_3 or

carboxy. The hydrophobic moiety may be linked via a spacer such as a C alkyl chain optionally interrupted with 1 or more (i.e. 1-4) heteroatoms, carbonyl or sulfonyl (SO) groups. More preferably, one of R and R is phenyl, cyclohexyl, indole, thienyl, quinoline, tetrahydroisoquinoline, naphthyl or benzodioxolane linked via C alkyl optionally interupted with a heteroatom or a carbonyl while the other is H, carboxymethyl or carboxyethyl.

Preferably, **A** is absent or CH.

Preferably, **B** is S or CH.

Preferably, **D** is CH.

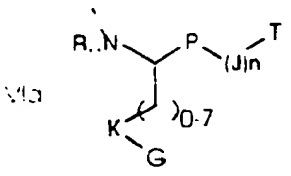
Preferably, **E** is CH substituted with -C(O)R wherein R is as previously defined.

Preferably, **X** is CH-R or N-R.

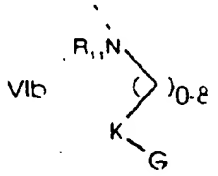
Preferably, **Y** is CH-R or S.

Preferably, **Z** is O.

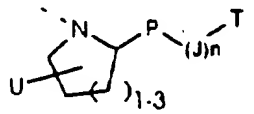
In a preferred embodiment, R_1 is represented by one of formula VIa to VId:



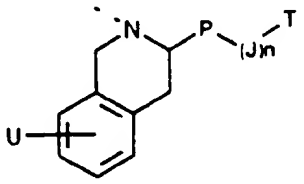
VIa



VIb



VIc



VId

wherein:

R_{11} is hydrogen or C alkyl;

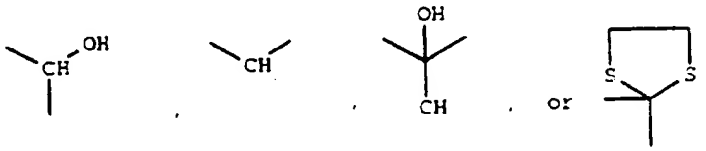
K is a bond or -NH-;

G is C alkoxy; cyano; -NH; -CH-NH; -C(NH)-NH; -NH-C(NH)-NH; -CH-NH-C(NH)-NH; a C cycloalkyl or aryl substituted with cyano, -NH, -CH-NH, -C(NH)-NH, -NH-

C(NH)-NH or -CH -NH-C(NH)-NH ; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, -NH , -CH -NH , -C(NH)-NH , -NH-C(NH)-NH or -CH -NH-C(NH)-NH ;

U is cyano, -NH , -C(NH)-NH or -NH-C(NH)-NH ;

P is a bond, -C(O)- or a bivalent group:



J is C alkylene optionally substituted with OH, NH and C alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C alkyl, C alkoxy, C aralkyl, or heterocycle optionally substituted.

Preferably R_{11} is H or methyl and most preferably H.

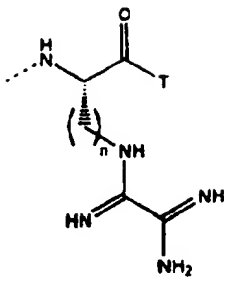
Preferably **K** is a bond.

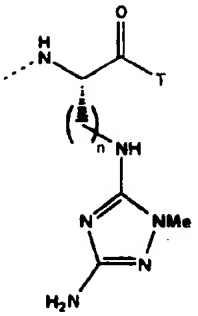
Preferably **G** is -NH-C(NH)-NH attached via a methylene chain of 3-7 carbons or phenyl substituted with -C(NH)-NH attached via a methylene chain of 0 to 3 carbons. More preferably G -NH-C(NH)-NH attached via a methylene chain of 3 atoms.

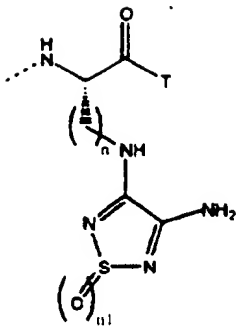
Preferably **P** is -C(O)-.

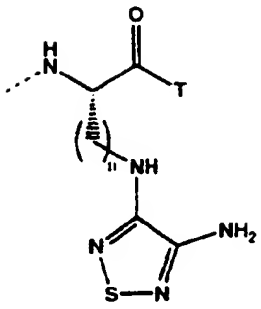
Preferably **J** is selected from: -CH -S-CH -CH -; -CH -O-CH -CH -; -CH -NH-CH -CH -; and a bond when n is 0. More preferably, J is a bond while n is 0.

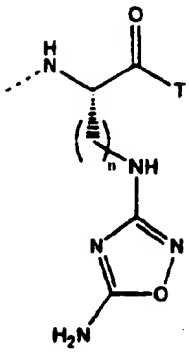
In particular embodiments of the invention, P is selected from the following amino acid derivatives prepared according to the procedures described in Bioorg. Med. Chem., 1995, 3:1145 :

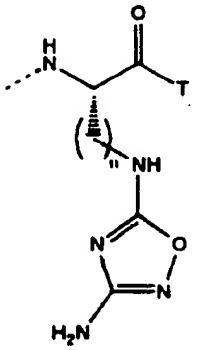


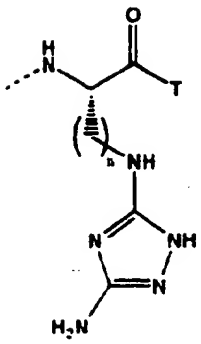


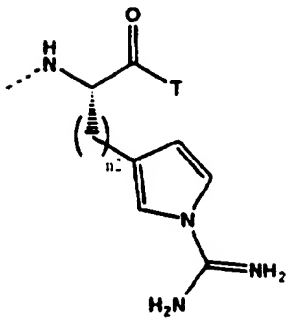


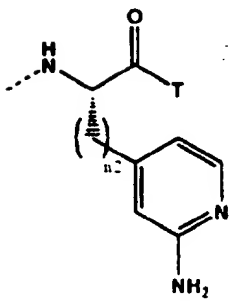


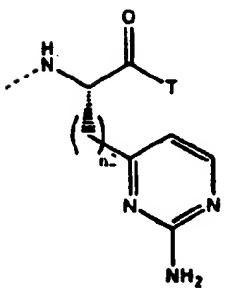


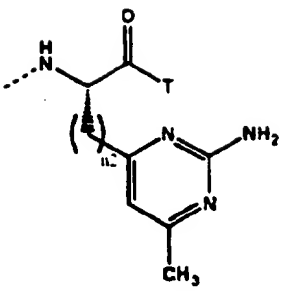


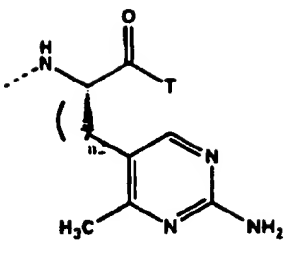












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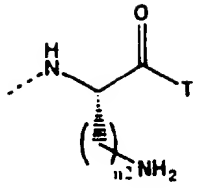
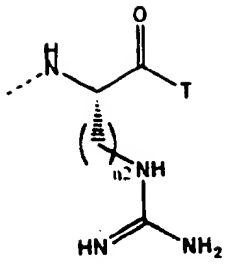
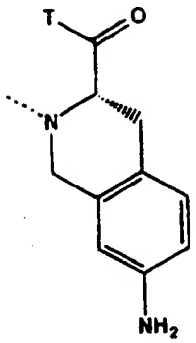
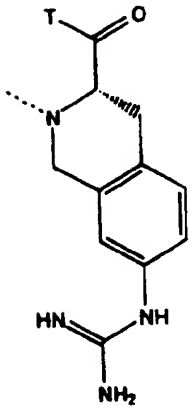
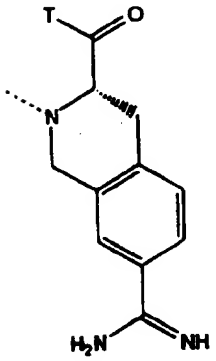
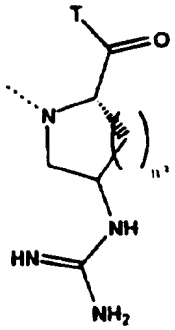
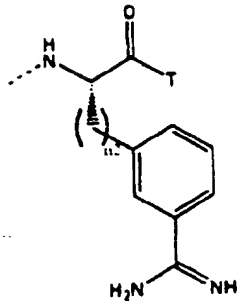
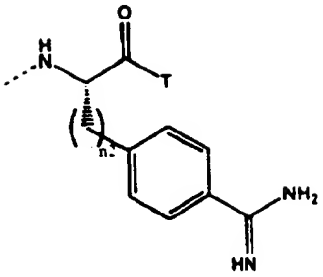
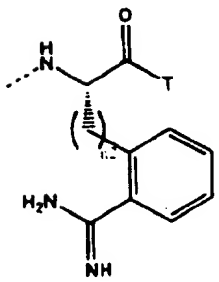

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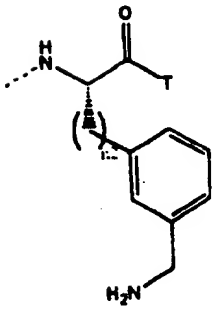
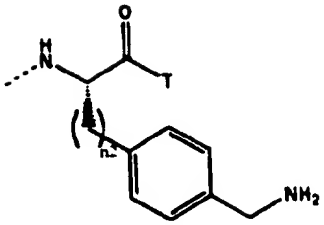
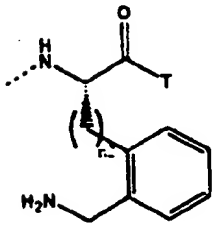
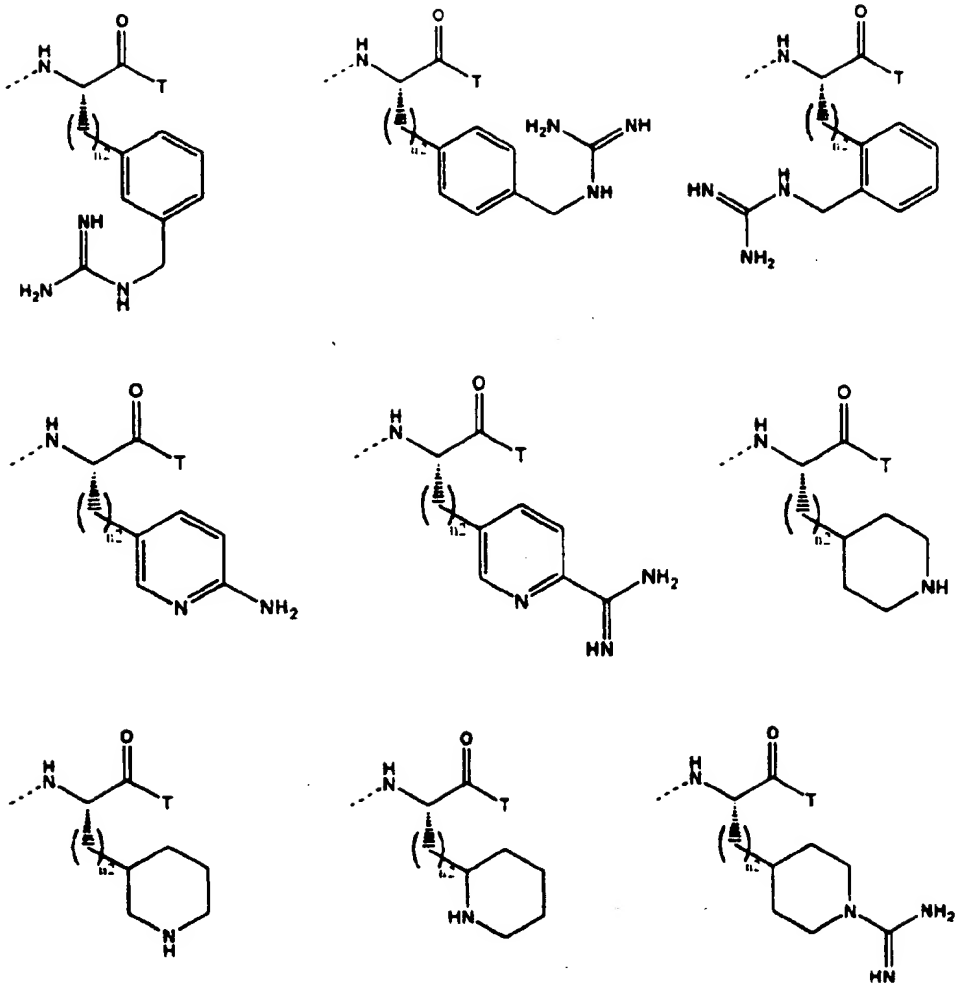
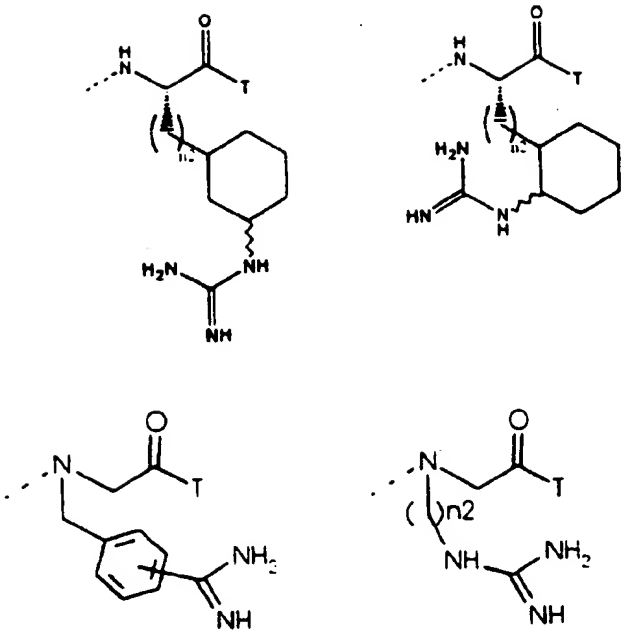
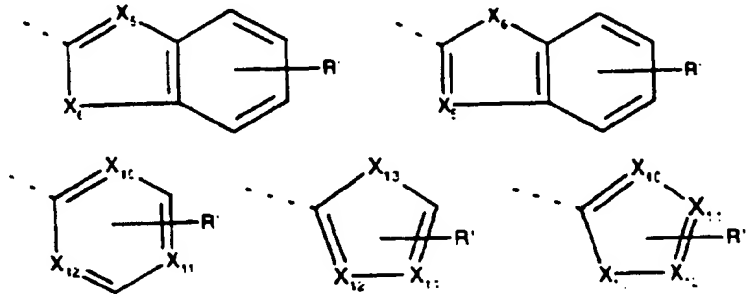








wherein n=1-6, n1=1-2, n2=0-7 and T is as previously defined.

In a preferred embodiment, **T** is a peptide of 1 to 4 amino acid residues in length and preferably fibrinogen's A or B chain or fragment or derivative thereof. In another preferred embodiment, T is a heterocycle selected from the group consisting of:



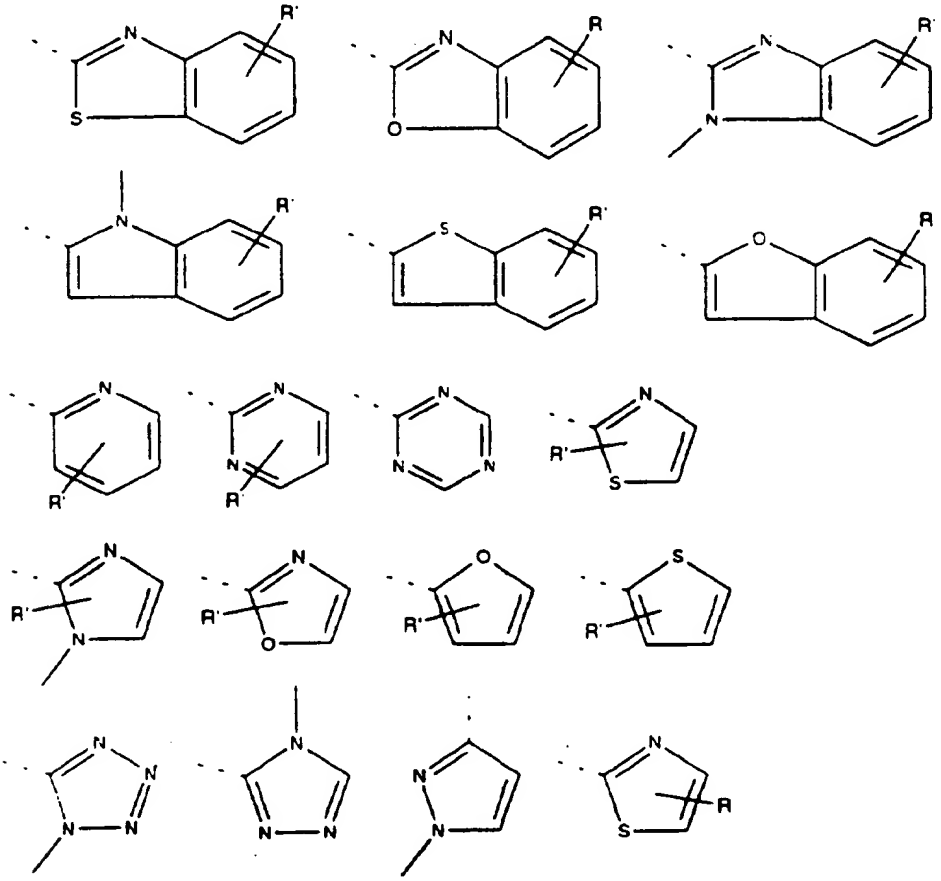
wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_x where X_x is hydrogen, C_{1-6} alkyl, or C_{6-10} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X, or CH-X;

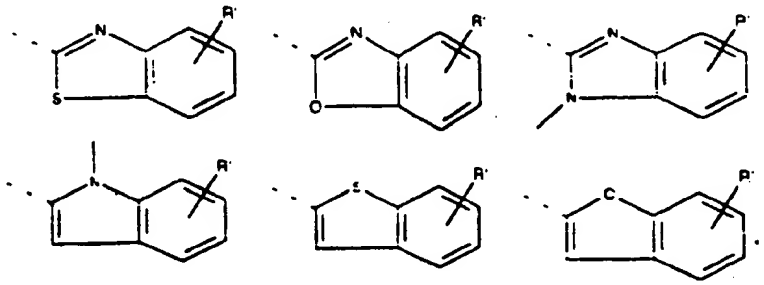
R' is hydrogen, C_{1-6} alkyl optionally carboxyl substituted, carboxyl, -C_{1-6} alkyl-CO-C_{1-6} alkyl, C_{7-9} aralkyl, C_{3-6} cycloalkyl, aryl or an aromatic heterocycle.

Preferably T is selected from the group consisting of:



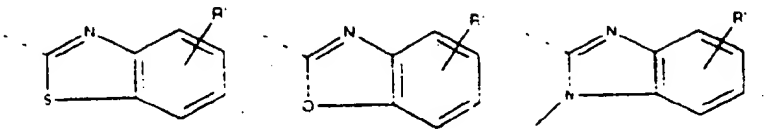
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



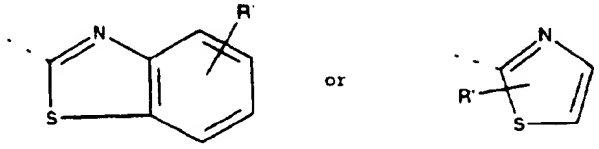
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



wherein R' is as defined above.

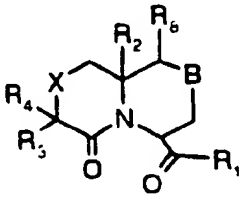
Most preferably T is



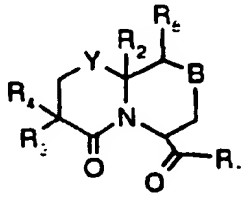
wherein R' is H or C alkyl such as methyl, ethyl, propyl or butyl and most preferably wherein R' is hydrogen,. In another embodiment, T is a 1,2 thiazole optionally substituted with R' and\or is attached to J at the 2, 3, 4 or 5 position of the ring.

In particular embodiments, compounds of the invention are represented by formulas II, III, IV and V, wherein X, Y, B, R to R and R are as previously defined.

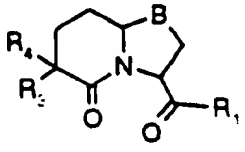
(II)



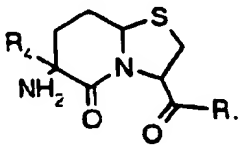
(III)



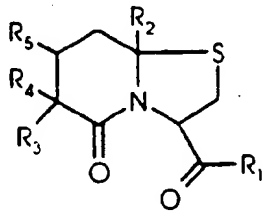
(IV)

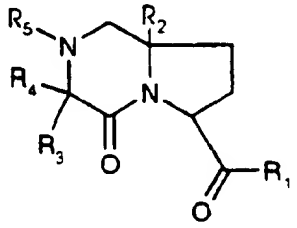


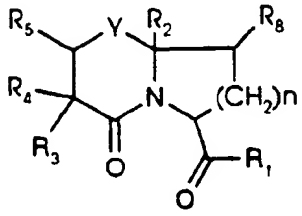
(V)

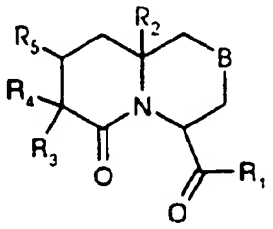


In a particularly preferred embodiment, compounds of the invention are represented by one of formulas VII, VIII, IX and X:

(VII) 

(VIII) 

(IX) 

(X) 

wherein

B is O, S, $-CH_2-$, or $-NH-$;

Y is selected from O, S, SO, SO_2, N-R_5 and CH-R_5;

R_1 is an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R_2 is H or C_{1-6} alkyl;

R_3 is selected from H, NR_6R_7 and C_{1-6} alkyl; and

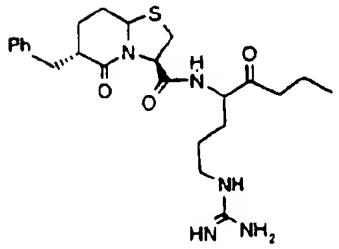
R_4 and R_5 are independently selected from H; NR_6R_7; C_{6-10} aryl or C_{3-8} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-6} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} aryl, heterocycle or C_{3-8} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group;

R_8 is hydrogen, C_{1-6} alkyl optionally interupted with 1 or 2 heteroatoms; C_{6-10} aryl, C_{3-8} cycloalkyl or heterocyclic ring or a hydrophobic group; and

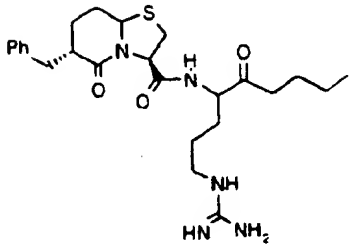
n is 1 or 2.

Preferred compounds according to formula VII include:

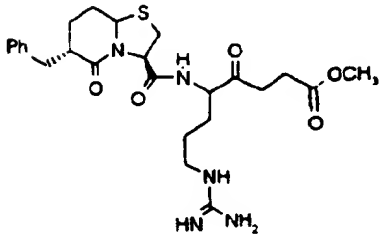
6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a] pyridine-3R-carboxamido (propyl ketoarginine)



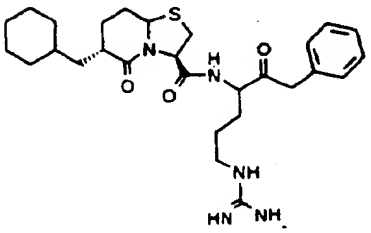
6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a] pyridine-3R-carboxamido (butyl ketoarginine)



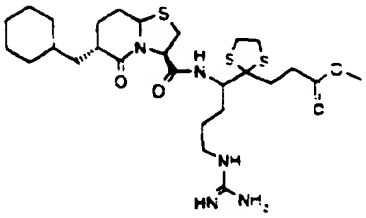
6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a] pyridine-3R-carboxamido(propylcarbmethoxy ketoarginine)



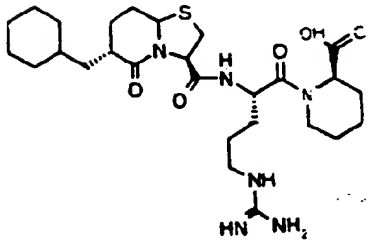
6S-cyclohexylmethyl hexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(benzylketo arginine)



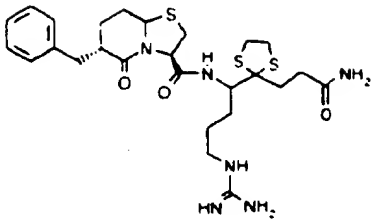
6S-cyclohexyl methyl hexahydro-5-oxo-5H-thiazolo[3,2-a)pyridine -3R-carboxamido(carbmethoxy propyl cyclodithioketalarginine)



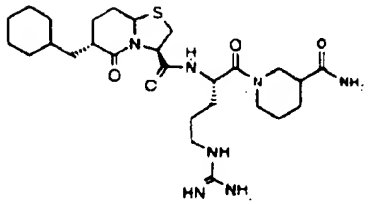
6S-cyclohexylmethyl hexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((S)-Arg-(R)-pipecolilic acid)



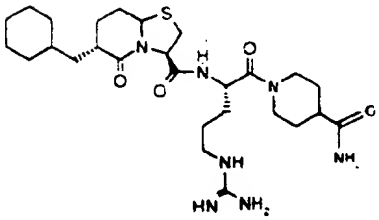
0035 6S-benzylhexa hydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido(carboxamidopropyl cyclodithioketal arginine)



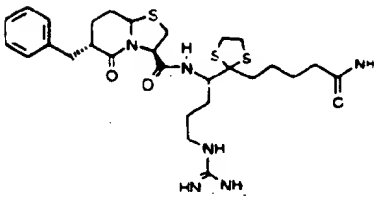
0040 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((S)-Arg nipecotamide)



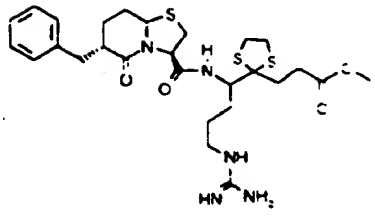
0045 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((S)Arg isonipecotamide)



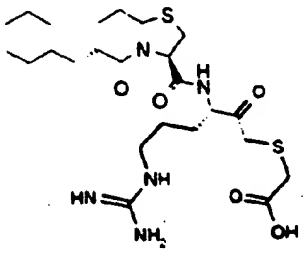
0050 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(carboxamidopentyl cyclodithioketal arginine)



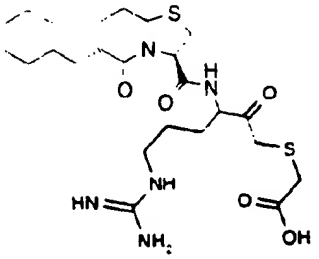
0055 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(carbmethoxy propyl cyclodithioketal arginine)



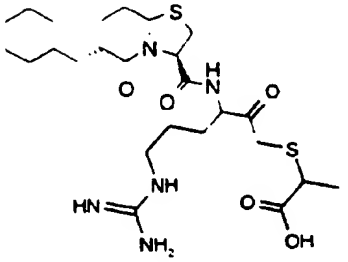
0060 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(1-carboxy-3-thiobutyl ketoarginine)



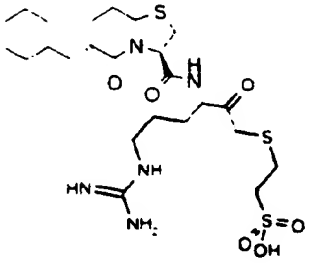
0065 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(1-carboxy-3-thiobutyl ketoarginine)



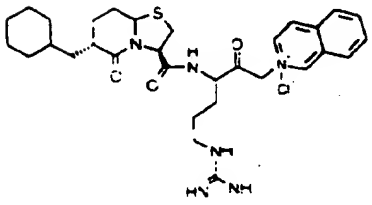
0070 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(1-carboxy-2-methyl-3-thiobutyl ketoarginine)



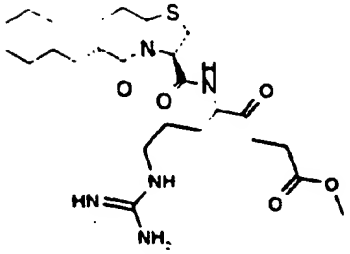
0075 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((3-thiobutyl sulfonic acid) ketoarginine)



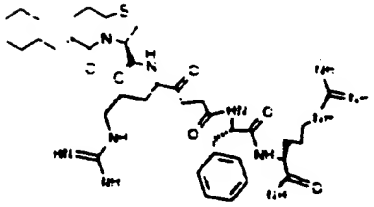
0080 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(iso-quinolinium methyl ketoarginine)



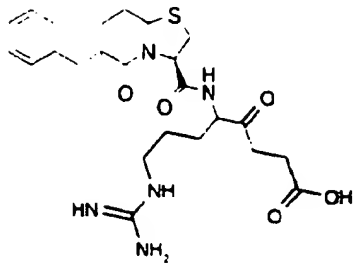
0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbmethoxy ketoarginine)



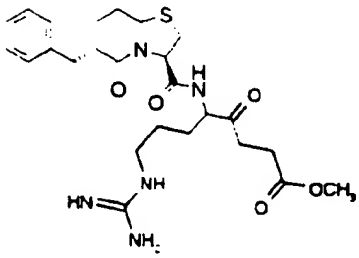
0090 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propylketo)Arg-Phe-Arg-NH_2)



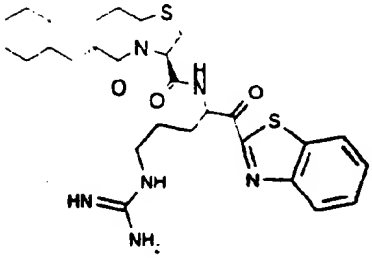
0095 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propanoic acid) ketoarginine)



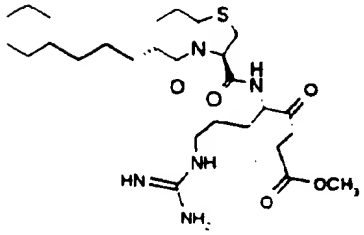
0100 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propyl carbmethoxy ketoarginine)



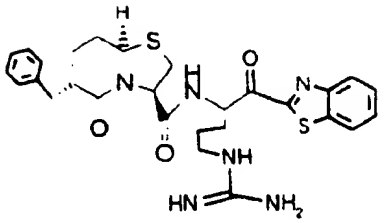
0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiazolo keto arginine); and



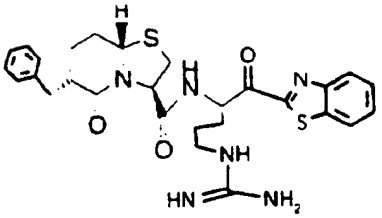
0110 6S-cyclohexylpropylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido(propylcarbmethoxy ketoarginine)



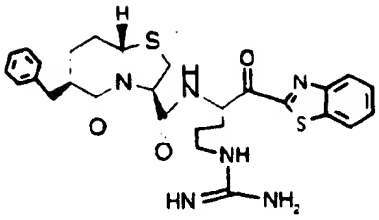
0205 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



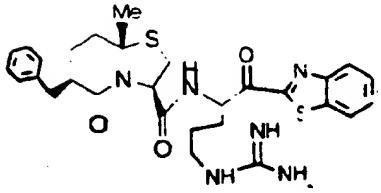
0210 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



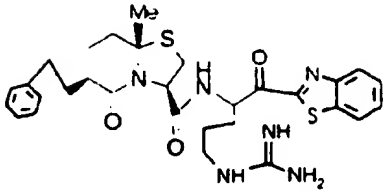
0215 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



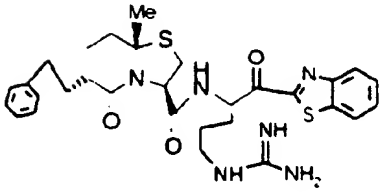
0220 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



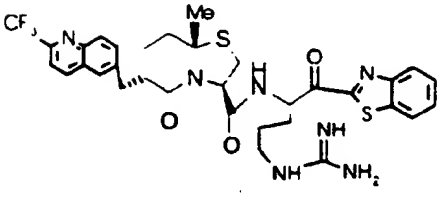
0225 8a-Methyl-5-oxo-6-phenethyl-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



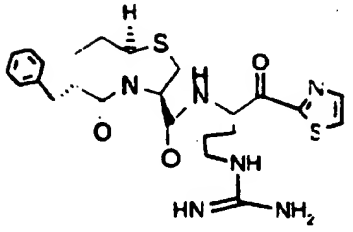
0230 8a-Methyl-5-oxo-6-phenethyl-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



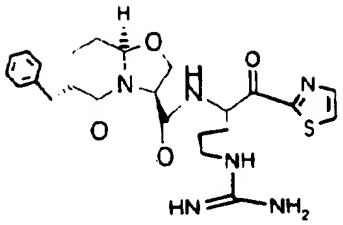
0240 8a-Methyl-5-oxo-6-(2-trifluoro methyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a] pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



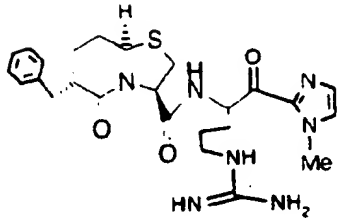
0245 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide



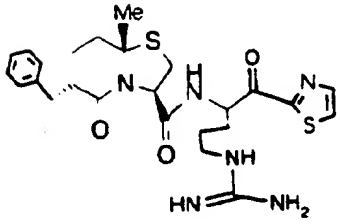
0250 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide



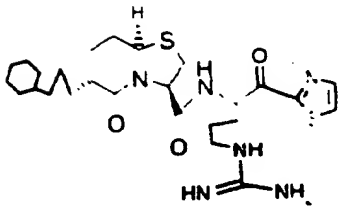
0255 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(1-methyl-1H imidazole-2-carbonyl)butyl]-amide



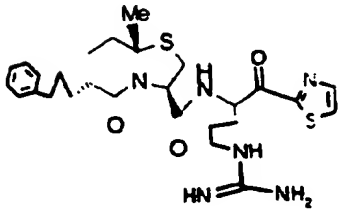
0260 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



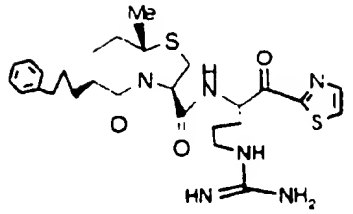
0265 5-Oxo-6-(3-cyclohexyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide



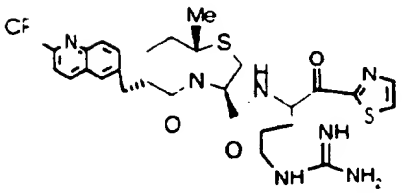
0275 8a-Methyl-5-oxo-6-(3-phenyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



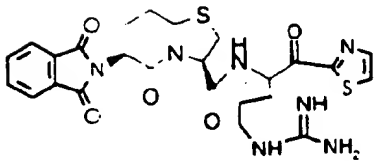
0280 8a-Methyl-5-oxo-6-(3-phenyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



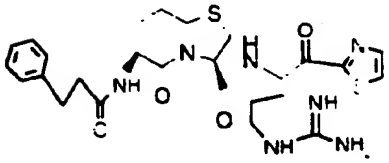
0285 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



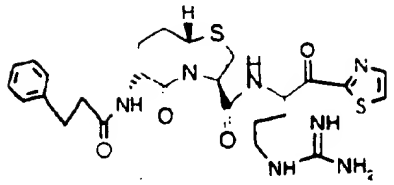
0295 6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0305 5-Oxo-6-(3-phenyl-propionyl amino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0315 5-Oxo-6-(3-phenyl-propionyl amino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



More preferred compounds according to formula (VII) include:

0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbo methoxyketoarginine);

0090 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propylketo)Arg-Phe-Arg-NH_2);

0095 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propanoic acid) ketoarginine);

0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiozolo keto arginine);

0210 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

0220 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;0240 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

0245 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide;

0260 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide;

0265 5-Oxo-6-(3-cyclohexyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide;

0285 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide; and

0315 5-Oxo-6-(3-phenyl-propionylamino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

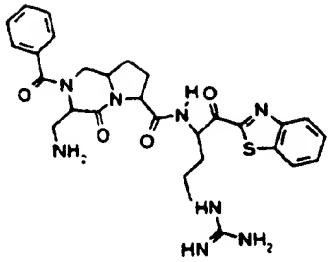
Most preferred compounds according to formula VII include:

0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbo methoxy ketoarginine); and

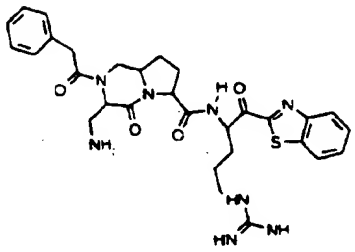
0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiozolo keto arginine).

Preferred compounds according to formula VIII include:

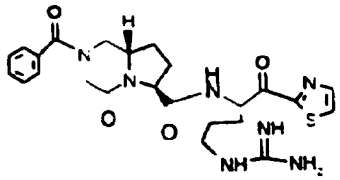
0325 3-Aminomethyl-2-benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyridine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



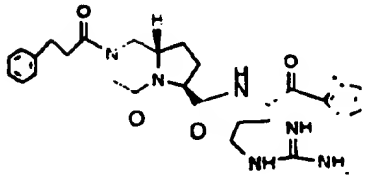
0330 3-Aminomethyl-4-oxo-2-phenylacetyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



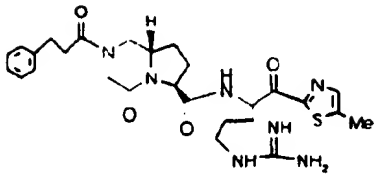
0335 2-Benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



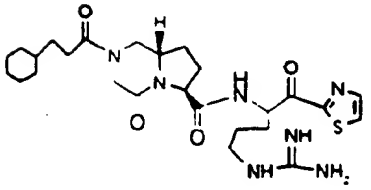
0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



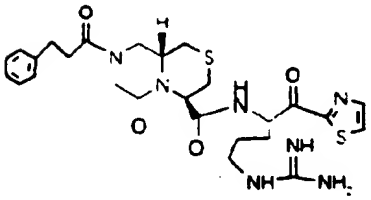
0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide



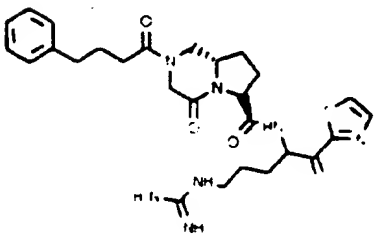
0350 2-(3-Cyclohexyl-propionyl)-4-oxo- octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(2-thiazole-carbonyl)-butyl]-amide



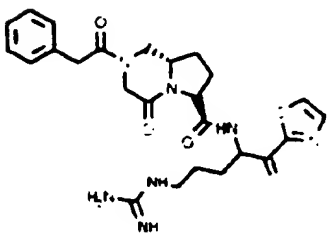
0355 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



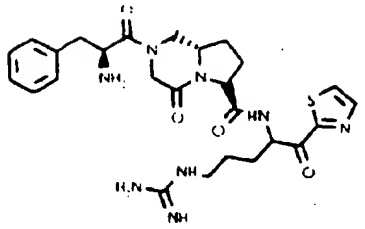
0365 4-Oxo-2-(4-phenyl-butyryl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



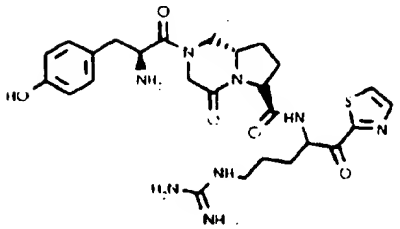
0370 4-Oxo-2-phenylacetyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



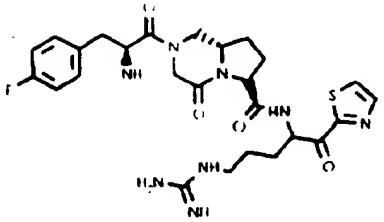
0375 2-(2-Amino-3-phenyl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



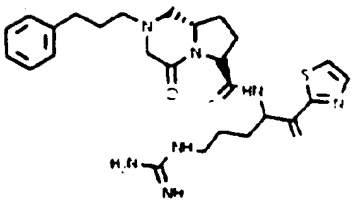
0380 2-[2-Amino-3-(4-hydroxy-phenyl)-propionyl]-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



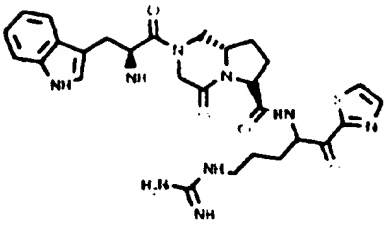
0385 2-[2-Amino-3-(4-fluoro-phenyl)-propionyl]-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



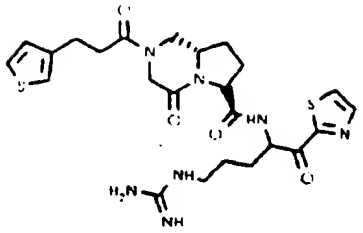
0390 4-Oxo-2-(3-phenyl-propyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



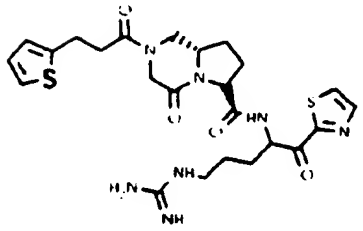
0395 2-[2-Amino-3-(1H-indol-3-yl)-propionyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



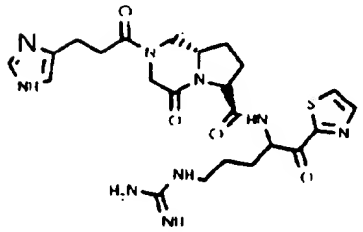
0400 4-Oxo-2-(3-thiophen-3-yl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



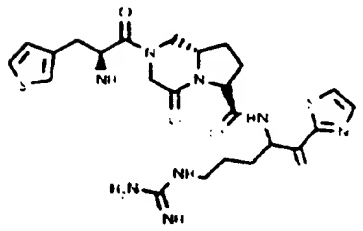
0405 4-Oxo-2-(3-thiophen-2-yl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



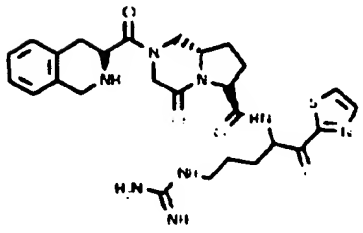
0410 2-(3-1 H-Imidazol-4-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



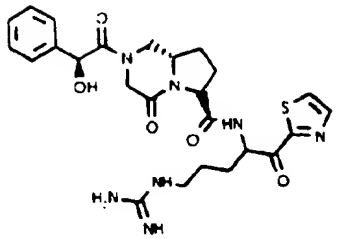
0415 2-(2-Amino-3-thiophen-3-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



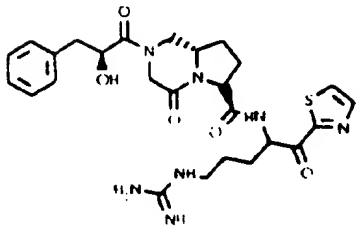
0420 4-Oxo-2-(1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



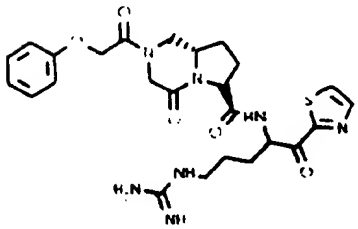
0425 2-(Hydroxy-phenyl-acetyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



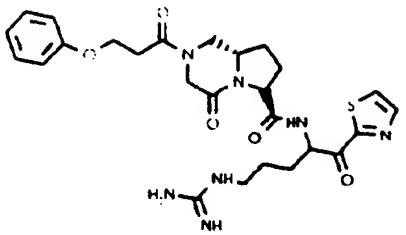
0430 2-(2-Hydroxy-3-phenyl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



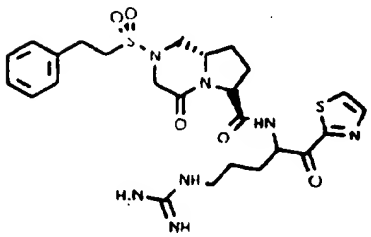
0435 4-Oxo-2-phenoxyacetyl-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



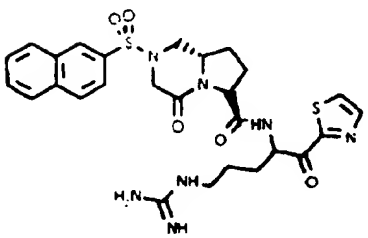
0440 4-Oxo-2-(3-phenoxy-propionyl)-ocatahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



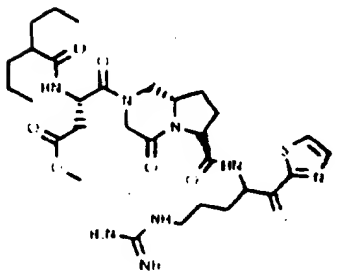
0445 4-Oxo-2-(2-phenyl-ethanesulfonyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazle-2-carbonyl)-butyl]-amide



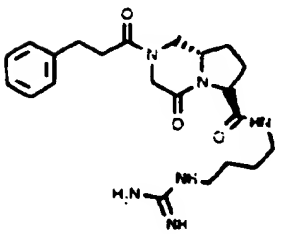
0450 2-(Naphthalene-2-sulfonyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



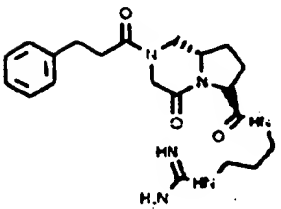
0455 4-(6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a] pyrazin-2yl)-4-oxo-3-(2 propyl -pentanoylamino)-butyric acid methyl ester



0460 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1)-butyl]-amide

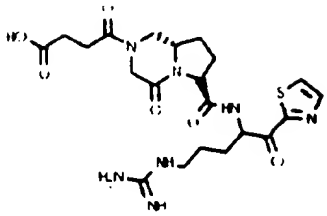


0465 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [3-guanidino-propyl) -amide

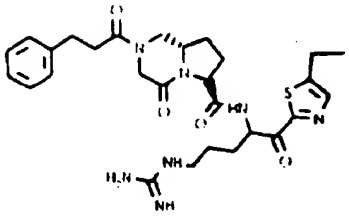


SUBSTITUTE SHEET

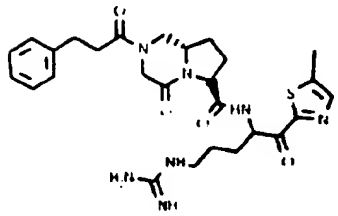
0470 4-(6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazin 2-yl)-4-oxo-butyric acid



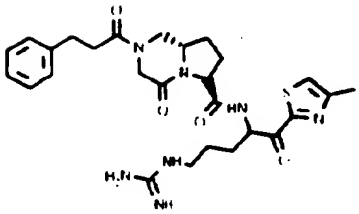
0475 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-ethyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide



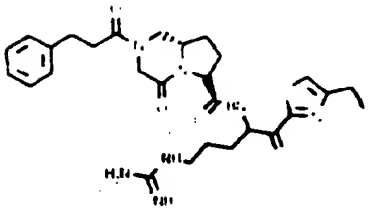
0480 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide



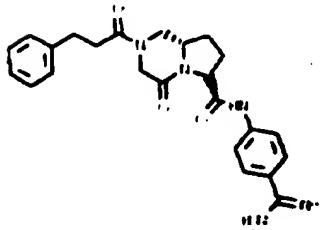
0485 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(4-methyl-thiazole-2-carbonyl)-butyl]-amide



0490 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid[1-(4-ethyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide

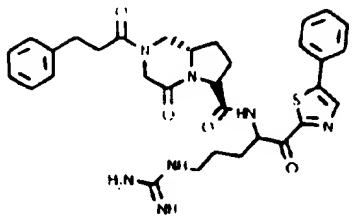


0495 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (4-carbamimidoyl-pheny)-amide

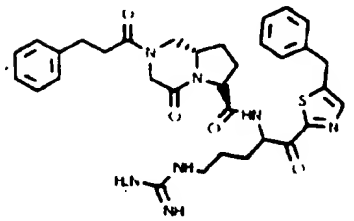


SUBSTITUTE SHEET

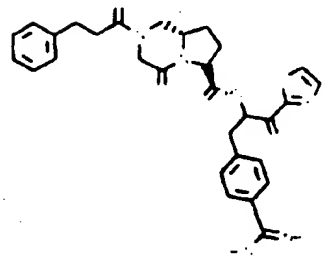
0500 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-phenyl-thiazole-2-carbonyl)-butyl]-amide



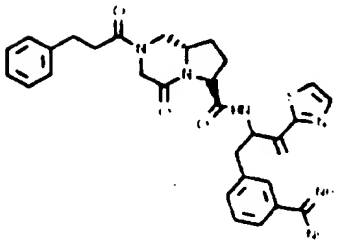
0505 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-benzyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide



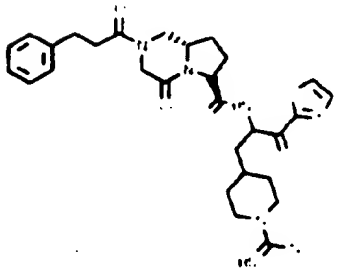
0510 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



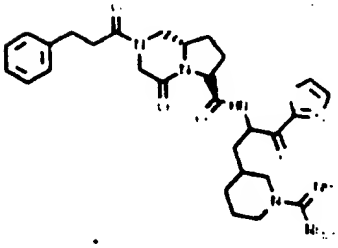
0515 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



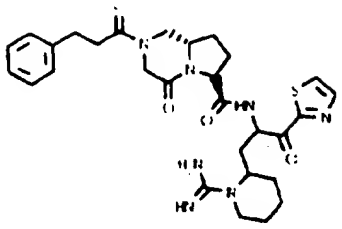
0520 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



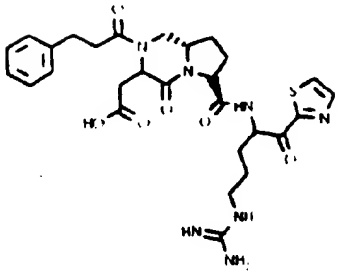
0525 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



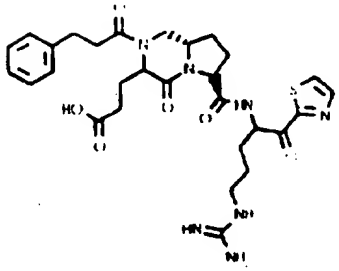
0530 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-2-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



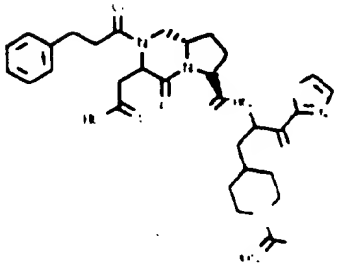
0535 [6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-3-yl]-acetic acid



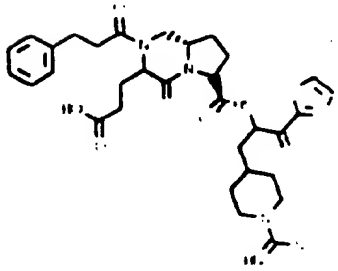
0540 3-[6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-propionic acid



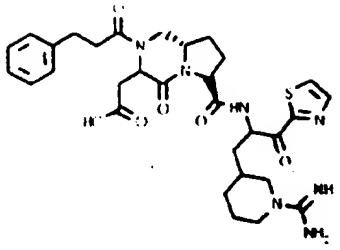
0545 [6-[1-(1-Carbamimidoyl-piperin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid



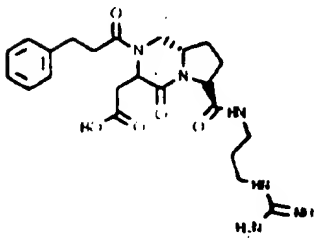
0550 3-[6-[1-(1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid



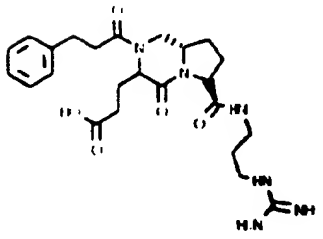
0555 [6-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid



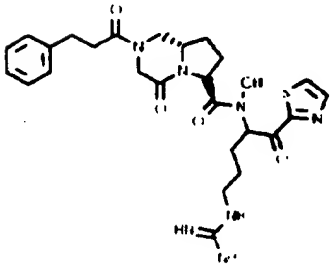
0560 [6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid



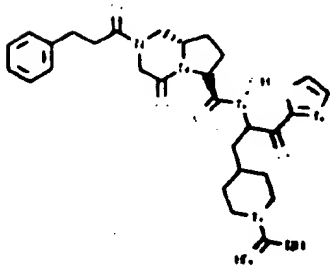
0565 3-[6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-propionic acid



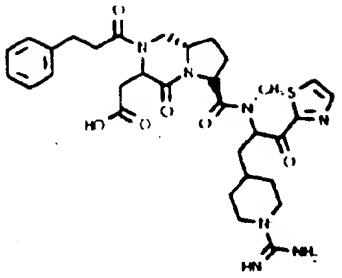
0570 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazolc-2-carbonyl)-butyl]-methyl-amide



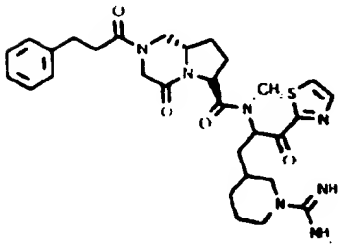
0575 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide



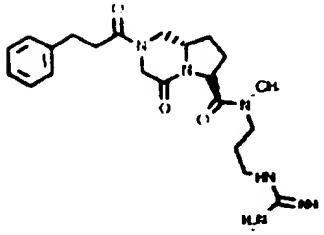
0580 [6-([1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-carbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic-acid



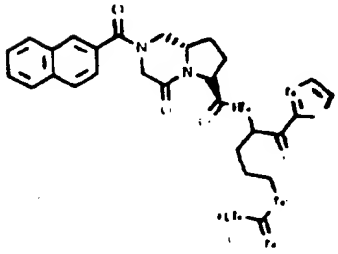
0585 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide



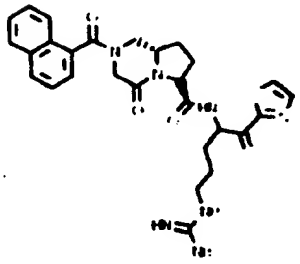
0590 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-methyl-amide



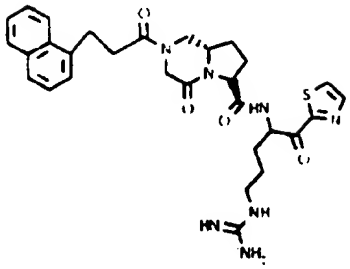
0595 2-(Naphthalene-2-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



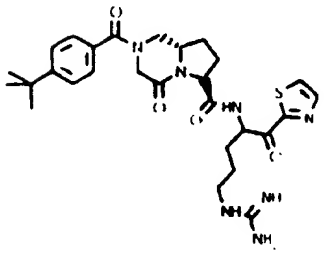
0600 2-(Naphthalene-1-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



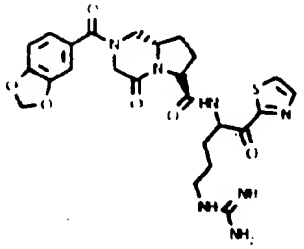
0605 2-(3-Naphthalen-1-yl-proplonyl)4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



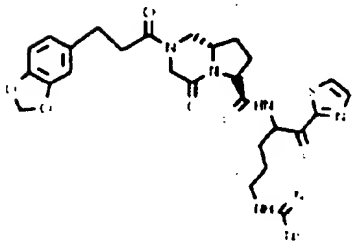
0610 2-(4-tert-Butyl-benzoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



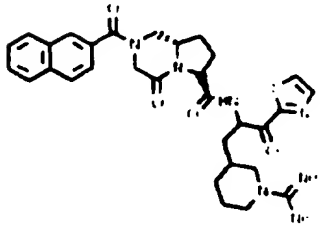
0615 2-(Benzo[1,3]dioxole-5-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



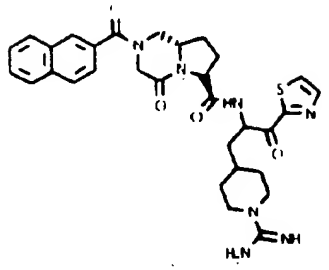
0620 2-(3-Benzo[1,3]dioxol-5-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



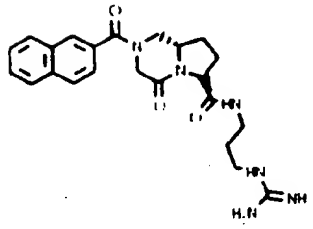
0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



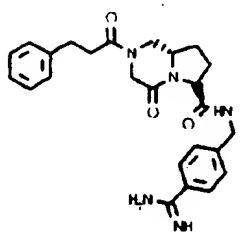
0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



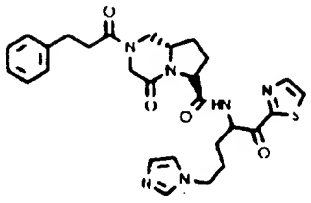
0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide



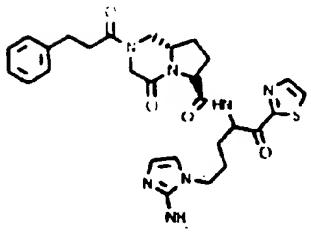
0640 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid 4-carbamimidoyl-benzylamide



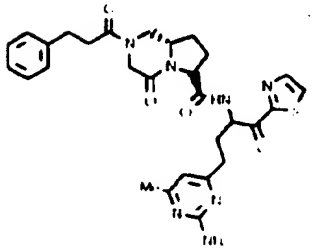
0645 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-imidazol-1-yl-1-(thiazole-2-carbonyl)-butyl]-amide



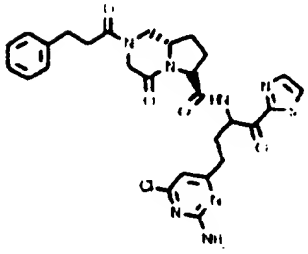
0650 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-(2-amino-imidazol-1-yl)-1-(thiazole-2-carbonyl)-butyl]-amide



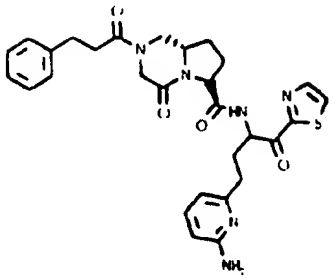
0655 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-methyl-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide



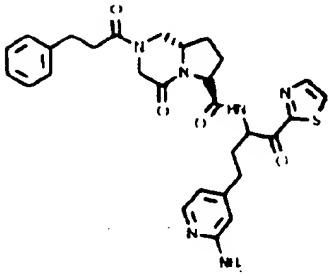
0670 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-chloro-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide



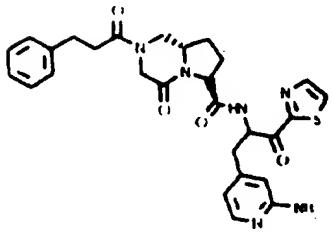
0675 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-propyl]-amide



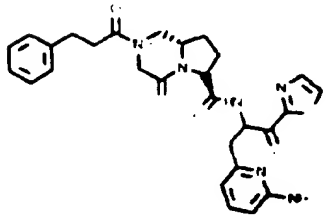
0680 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide



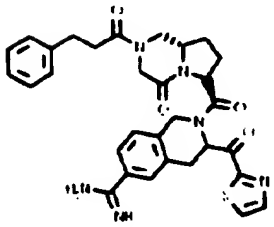
0685 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide



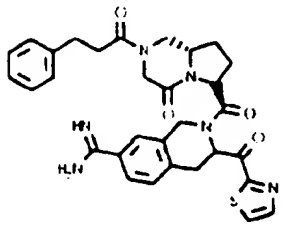
0690 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide



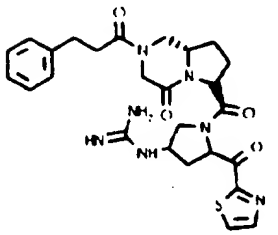
0695 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-6-carboxamidine



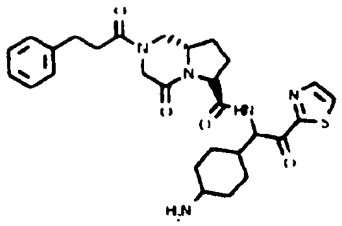
0700 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carboxamidine



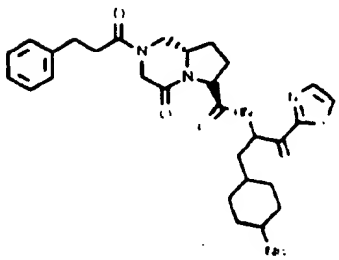
0705 N-[1-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-5-(thiazole-2-carbonyl)-pyrrolidin-3-yl]-guanidine



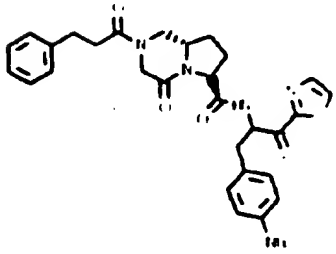
0710 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



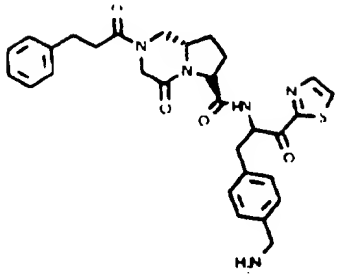
0715 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



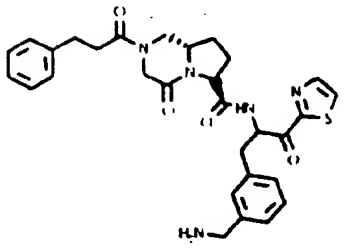
0720 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



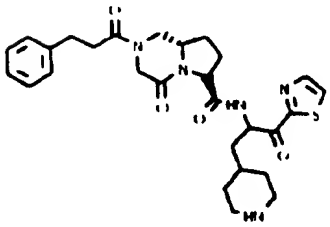
0725 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-aminomethyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



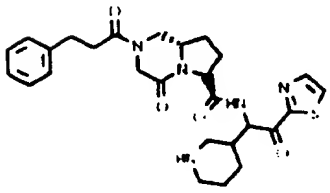
0730 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-aminomethyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



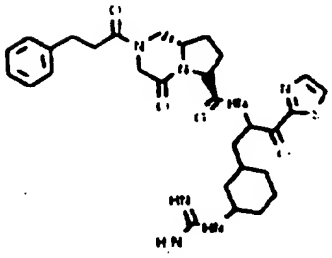
0735 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (2-oxo-1-piperidin-4-ylmethyl-2-thiazol-2-yl-ethyl)-amide



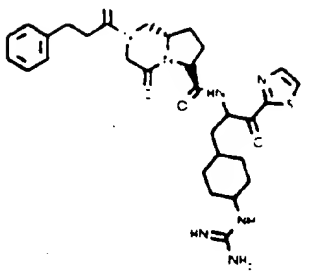
0740 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (2-oxo-1-piperidin-3-yl-2-thiazol-2-yl-ethyl)-amide



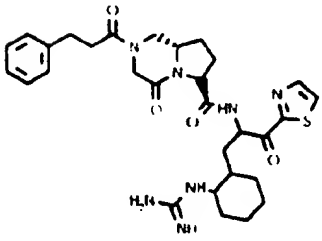
0745 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



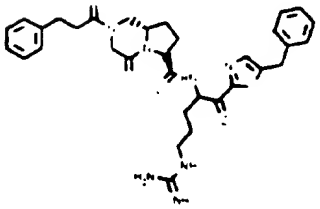
0750 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



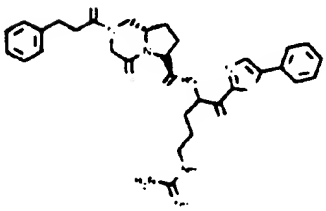
0755 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(2-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



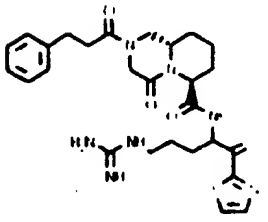
0760 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-benzyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide



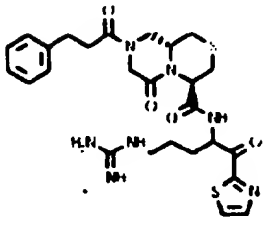
0765 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-phenyl-thiazole-2-carbonyl)-butyl]-amide



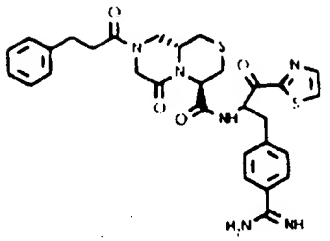
0770 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrido[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



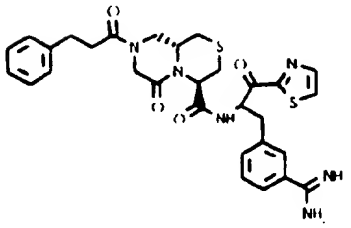
0775 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



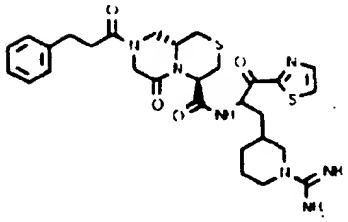
0780 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(4-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



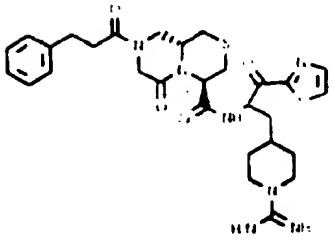
0785 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



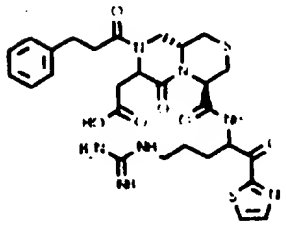
0790 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



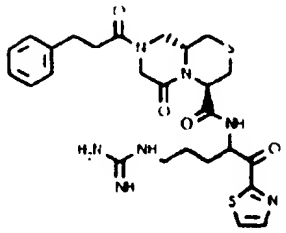
0795 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



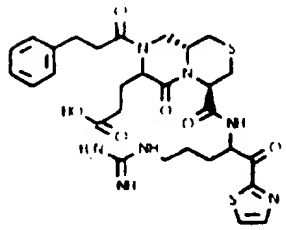
0800 [4-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-5-oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalen-6-yl]-acetic acid



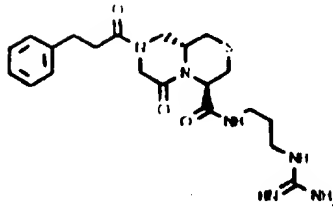
0805 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



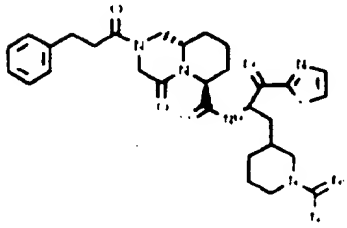
0810 3-[4-[4-Guanidino-1-(thiazole-2-carbonyl-butylcarbamoyl]-5-oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalen-6-yl]-propionic acid



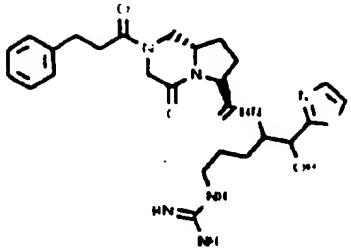
0815 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [3-guanidino-propyl]-amide



0820 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



0825 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(hydroxy-thiazol-2-yl-methyl)-butyl]-amide



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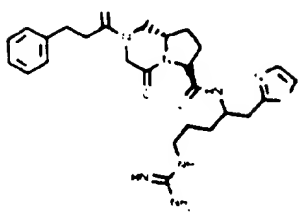
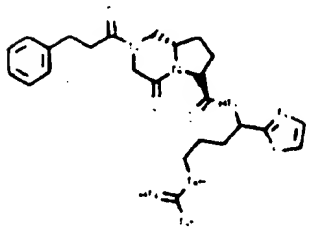
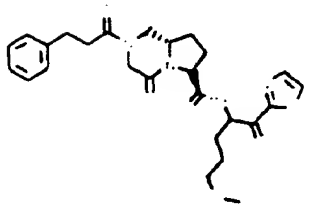
0830 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (4-guanidino-1-thiazol-2-ylmethyl-butyl)-amide



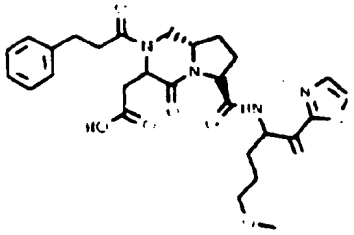
0835 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-thiazol-2-yl-butyl)-amide



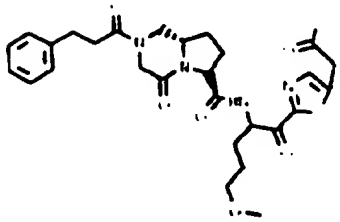
0840 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-methoxy-1-(thiazole-2-carbonyl)-butyl]-amide



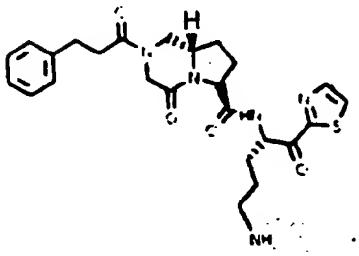
0845 [6-[4-Methoxy-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic acid



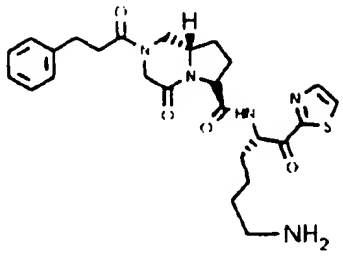
0850 [2-(5-Methoxy-2-([4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino)-pentanoyl)-thiazol-5-yl]-acetic acid



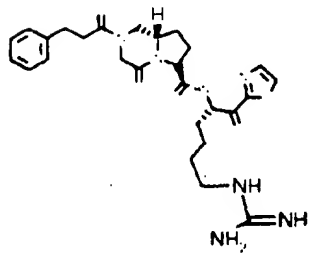
0855 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-amino-1-(thiazole-2-carbonyl)-butyl]-amide



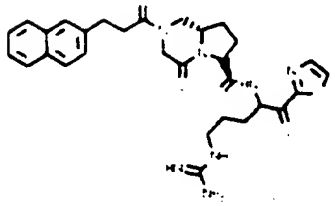
0860 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-amino-1-(thiazole-2-carbonyl)-pentyl]-amide



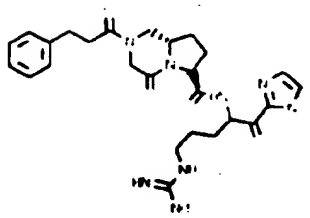
0865 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-guanidino-1-(thiazole-2-carbonyl)-pentyl]-amide



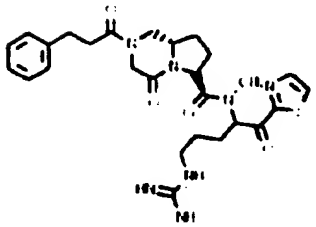
0870 2-(3-Naphthalen-2-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



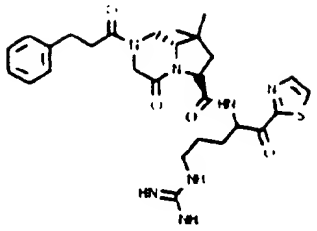
0875 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(1-methyl-1H-imidazole-2-carbonyl)-butyl]-amide



0880 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0885 8,8-Dimethyl-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



Preferred compounds according to formula (VIII) include:

0325 3-Aminomethyl-2-benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyridine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

0330 3-Aminomethyl-4-oxo-2-phenylacetyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

0515 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0530 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-2-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0545 [6-[1-(1-Carbamimidoyl-piperin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0550 3-[6-[1-(1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0555 [6-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0560 |6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0565 3-|6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-propionic acid

0575 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid |1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide

0580 |6-(|1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-carbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic-acid

0585 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid |1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide

0590 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-methyl-amide

0595 2-(Naphthalene-2-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid |4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide

0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide

0645 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-imidazol-1-yl-1-(thiazole-2-carbonyl)-butyl]-amide

0670 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-chloro-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

0675 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

0680 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

0685 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide

0690 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide

0695 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-6-carboxamidine

0700 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carboxamidine

0705 N-[1-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-5-(thiazole-2-carbonyl)-pyrrolidin-3-yl]-guanidine